Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Gastroenterología y Hepatología 46 (2023) 425–438

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Gastrointestinal symptoms and complications in patients hospitalized due to COVID-19, an international multicentre prospective cohort study (TIVURON project)

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Abbreviations: aOR, adjusted odds ratio; ACE2, angiotensin-converting enzyme 2; ARBs, angiotensin II receptor blockers; AUC, areas under the curve; Cis, confidence intervals; COVID-19, coronavirus disease; CRP, C-reactive protein; GI, gastrointestinal; ICU, intensive care unit; IL-6, interleukin-6; IQR, interquartile range; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; ROC, receiver operating characteristic; Se, sensibility; SOFA, sepsis-related organ failure assessment; SARS, severe acute respiratory syndrome; SARS-CoV2, severe acute respiratory syndrome coronavirus; SAG, Spanish Association of Gastroenterology; Sp, specificity; SD, standard deviation; TMPRSS2, transmembrane protease serine 2; WHO, World Health Organization.

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Received 8 August 2022; accepted 5 October 2022
Available online 13 October 2022

KEYWORDS
COVID-19;
Gastrointestinal symptoms;
Gastrointestinal complications;
Hospitalization;
Hepatitis

Abstract:
Background: Retrospective studies suggest that coronavirus disease (COVID-19) commonly involves gastrointestinal (GI) symptoms and complications. Our aim was to prospectively evaluate GI manifestations in patients hospitalized for COVID-19.
Methods: This international multicentre prospective cohort study recruited COVID-19 patients hospitalized at 31 centres in Spain, Mexico, Chile, and Poland, between May and September 2020. Patients were followed-up until 15 days post-discharge and completed comprehensive questionnaires assessing GI symptoms and complications. A descriptive analysis as well as a bivariate and multivariate analysis were performer using binary logistic regression. $p < 0.05$ was considered significant.
Results: Eight hundred twenty-nine patients were enrolled; 129 (15.6%) had severe COVID-19, 113 (13.7%) required ICU admission, and 43 (5.2%) died. Upon admission, the most prevalent GI symptoms were anorexia ($n = 413$; 49.8%), diarrhoea ($n = 327$; 39.4%), nausea/vomiting ($n = 227$; 27.4%), and abdominal pain ($n = 172$; 20.7%), which were mild/moderate throughout the disease and resolved during follow-up. One-third of patients exhibited liver injury. Non-severe COVID-19 was associated with $\geq$2 GI symptoms upon admission (OR 0.679; 95% CI 0.464–0.995; $p = 0.046$) or diarrhoea during hospitalization (OR 0.531; 95% CI 0.328–0.860; $p = 0.009$). Multivariate analysis revealed that worse hospital outcomes were not independently associated with liver injury or GI symptoms.
Conclusion: GI symptoms were more common than previously documented, and were mild, rapidly resolved, and not independently associated with COVID-19 severity. Liver injury was a frequent complication in hospitalized patients not independently associated with COVID-19 severity.

PALABRAS CLAVE
COVID-19;
Síntomas gastrointestinales;
Complicaciones gastrointestinales;
Hospitalización;
Hepatitis

Síntomas y complicaciones gastrointestinales en pacientes hospitalizados por COVID-19, estudio internacional, multicéntrico, de cohorte, prospectivo (proyecto TIVURON)

Resumen:
Antecedentes: Estudios retrospectivos evidencian que la enfermedad por coronavirus (COVID-19) conlleva síntomas y complicaciones gastrointestinales (GI). Nuestro objetivo fue evaluar prospectivamente las manifestaciones GI de pacientes hospitalizados por COVID-19.
Métodos: Estudio internacional, multicéntrico, de cohorte, prospectivo, que seleccionó a pacientes con COVID-19 en 31 centros de España, México, Chile y Polonia, entre mayo-septiembre de 2020. Los pacientes fueron seguidos hasta 15 días tras el alta y completaron cuestionarios que evaluaban los síntomas y complicaciones GI. Se realizó un análisis descriptivo, bivariante y multivariante de los resultados. Se consideró significativa $p < 0,05$.
Resultados: Se incluyeron 829 pacientes; 129 (15,6%) presentaron COVID-19 grave, 113 (13,7%) requirieron ingreso en UCI y 43 (5,2%) fallecieron. Al ingreso, los síntomas GI más prevalentes fueron anorexia (n = 413; 49,8%), diarrea (n = 327; 39,4%), náuseas/vómitos (n = 227; 27,4%) y dolor abdominal (n = 172; 20,7%), que resultaron de intensidad leve/moderada y se resolvieron durante el seguimiento. Un tercio de los pacientes presentaron daño hepático. La COVID-19 no grave se asoció con la presencia de $\geq$2 síntomas GI al ingreso (OR 0,679; IC 95%: 0,464-0,995; p = 0,046) y/o diarrea durante la hospitalización (OR 0,531; IC 95%: 0,328-0,860; p = 0,009). El análisis multivariante reveló que los peores resultados hospitalarios no se asociaron de forma independiente con el daño hepático o los síntomas GI.
Conclusión: Los síntomas GI fueron más frecuentes de lo que se había documentado, resultaron leves, se resolvieron rápidamente y no se asociaron de forma independiente con COVID-19 grave. El daño hepático fue una complicación frecuente en los pacientes hospitalizados que no se asoció de forma independiente con COVID-19 grave.

Introduction

The initial reports describing COVID-19 disease highlighted respiratory symptoms, fever, and severe acute respiratory syndrome (SARS).[1,2] However, further several published retrospective studies and systematic reviews suggest that infected patients commonly exhibit GI symptoms, like diarrhoea, nausea, emesis, abdominal pain, and less specific symptoms, such as anorexia.[2–5] The virus can penetrate and infect epithelial gastrointestinal (GI) cells due to their surface expression of angiotensin-converting enzyme 2 (ACE2) receptors and the transmembrane protease serine 2 (TMPRSS2) used for S protein priming.[6] Moreover, this explains the detection of virus RNA in faecal samples, and potential changes in GI flora.[7,8]

Although GI symptoms are recognized within the spectrum of COVID-19 manifestations, the described frequency has widely varied, ranging from 3 to 50%.[3–5] Unfortunately, most of published studies are retrospective and have not evaluated the baseline pre-COVID-19 presence of GI symptoms. Moreover, virtually no prospective data are available describing the patient-assessed symptom intensity or their evolution throughout the disease.

Regarding GI complications, liver damage has been reported in approximately 15–35% of patients with COVID-19, especially in critically ill patients.[3–5,9] The mechanism underlying this liver damage has not been defined, although a multifactorial origin is postulated, which includes cytopathic effects of the virus, drug-related hepatotoxicity, immune-mediated liver damage, and critical involvement of the patient's liver.[10] Other possible GI complications of COVID-19 include acute pancreatitis,[11] new-onset inflammatory bowel disease,[12] and digestive ischaemic conditions secondary to endotheliitis, hypercoagulability, and systemic inflammation,[13,14] such as ischaemic colitis[15] or gangrenous cholecystitis.[16] However, it is difficult to establish a causal relationship due to biases associated with retrospective studies and the low incidence rates of these complications in the epidemiological context of high COVID-19 occurrence.[17]

In this international, multicentre, prospective cohort study, we aimed to describe the frequency, intensity, evolution, and impact of digestive symptoms and complications, during hospitalization and after discharge, in patients with COVID-19.

Methods

The prospecTIVe evalUation of gastROintestinal maNifestations of COVID-19 (TIVURON) project was an international, multicentre, prospective, cohort study, developed with the auspice of the Spanish Association of Gastroenterology (AEG). This study was conducted through the collaboration of 31 centres from Spain, Mexico, Chile, and Poland. Patients were recruited from May to September of 2020. The study was approved on May 6th of 2020 (reference PI2020-068) by the central Institutional Review Board (IRB) (Dr. Balmis General University Hospital CEiM, Alicante, Spain), and subsequently by the IRB of each participating centre. Informed

consent from patients was required. The STROBE guidelines were followed.

Study end-points

The primary outcome was the prevalence and intensity of GI symptoms and complications in patients hospitalized with COVID-19, as well as their evolution throughout the disease. Secondary outcomes included the associations of GI symptoms and complications with COVID-19 severity and hospital outcomes (hospital stay, need for ICU admission, and mortality).

Patient selection

Inclusion criteria were age ≥18, positive polymerase chain reaction (PCR) test for SARS-CoV-2 in any biological sample, hospital admission, and informed consent to participate in the study. Exclusion criteria were hospital admission due to a non-gastrointestinal disease clearly not related to COVID-19 (e.g., a hip fracture) with a subsequent diagnosis of COVID-19, acute active digestive disease clearly independent of COVID-19 (e.g., choledocholithiasis), acute outbreak of chronic inflammatory digestive disease (e.g., exacerbated chronic pancreatitis) with no apparent relationship to COVID-19, pre-existing digestive or non-digestive active neoplastic disease with abdominal or pelvic involvement, previous admission for COVID-19, or patients recruitment over 72 h after admission.

Gastrointestinal symptoms selection

Based on a previously published patient-reported outcome scale,[18] a survey was conducted among all collaborating researchers to assess the appropriateness of symptoms to be included in the study, using a numerical scale of 0–10, with 0 indicating no appropriateness, and 10 maximum appropriateness. The mean value for each symptom was calculated, and selected those with an average score of ≥5. Finally, the following nine symptoms were chosen: abdominal pain, gas/bloating/flatulence, diarrhoea, constipation, heartburn/gastroesophageal reflux, nausea/vomiting, hyporexia/anorexia, odynophagia, and dysphagia.

Data acquisition and definitions

Information regarding demographic features (including sex, understood as biological sex); toxic habits; previous comorbidities; chronic treatments; pre-COVID-19 GI symptoms; complications; analytical, radiological, and endoscopic data during admission; specific COVID-19 treatments; ventilatory support; mortality; and hospital stay, were collected. Data were prospectively acquired by researchers involved in direct patient management. Comprehensive symptom questionnaires were completed at different times throughout the disease course. A questionnaire administered at admission asked about GI symptoms at baseline (before COVID-19), and specifically at the time of admission. A questionnaire administered at discharge asked about the presence and higher intensity of GI symptoms during hospitalization, and specifically at the time of discharge. A final interview was performed at 15 days after discharge by phone call, asking about the presence and higher intensity of GI symptoms from discharge to the end of follow-up, and specifically at the time of interview.

The intensity of GI symptoms was defined as mild, moderate, or severe according to the patient's perception. Severe COVID-19 was defined as requiring ICU admission, requiring mechanical ventilation, and/or causing mortality during hospitalization, as previously reported by Colmenero et al.[19] The GI complications evaluated during COVID-19 hospitalization and convalescence included esophagitis, oesophageal-gastric-duodenal ulcers, gastritis, duodenitis, acute pancreatitis, acute liver injury, acute liver failure, cholecystitis, cholangitis, enteritis, colitis, and upper or lower gastrointestinal bleeding. Definitions are presented in supplementary content 1.

Sample size

As retrospective reports suggested a high incidence of GI symptoms and complications among COVID-19 patients, here we aimed to provide exploratory high-quality data. However, this observational descriptive study was performed under exceptional circumstances, with a global pandemic collapsing hospital care. Therefore, we did not perform a sample size calculation based on expectations of finding statistically significant differences. Rather, the final sample size depended on the capacities of the centres involved and the time-frame established for data collection.

Statistical analysis

Statistical analyses were performed using IBM-SPSS V 25.0 software (IBM, Armonk, NY, USA). Quantitative variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), and qualitative variables as number and percentage. Normality was assessed using the Shapiro–Wilk test. Quantitative variables were compared with qualitative variables using Student's *t*-test and the Mann–Whitney *U*-test for two categories, or using ANOVA and Kruskal–Wallis tests for over two categories. Qualitative variables were compared using the Chi-square test or Fisher's exact test if needed.

The Wilcoxon signed-rank test with continuity correction was used to make pairwise comparisons for each GI symptom at the five evaluated time-points, determining the difference compared to baseline GI symptoms (before COVID-19). Multivariate analysis was performed with binary logistic regression. Prevalence, odds ratio (OR), and adjusted odds ratio (aOR) with 95% confidence intervals (CIs) were calculated as measures of the frequency and strength of association. The Nagelkerke R^2 statistic was calculated to assess the proportion of variance of the dependent variable explained by the model. For bivariate and multivariate models, GI symptoms during hospitalization were considered with adjustment according to baseline (before COVID-19), with the analysis excluding patients who presented the GI symptom before COVID-19. The multivariate models included the patients' baseline characteristics, Charlson

Comorbidity Index adjusted by age, GI and non-GI symptoms, GI complications, Sepsis-related organ failure assessment (SOFA) score, and C-reactive protein (CRP) level as a marker of systemic inflammation. A p-value of <0.05 was considered statistically significant.

Results

This study enrolled a total of 829 hospitalized patients, including 486 (58.6%) from Spain, 203 (24.5%) from Mexico, 97 (11.7%) from Chile, and 43 (5.2%) from Poland. The median age was 57 years (IQR 44–70 years), 481 (58.0%) were male, and the median Charlson Comorbidity Index adjusted per age was 2 points (IQR 0–4 points). Table 1 shows the patients' baseline characteristics. Male gender, Charlson score, diabetes, and moderate-to-severe chronic renal disease were associated with severe COVID-19. The median time from symptom onset to admission was 7 days (IQR 4–10 days), and the median hospitalization length was 8 days (IQR 5–12 days). A total of 129 (15.6%) patients had severe COVID-19, 113 (13.7%) required ICU admission after a median of 1 day (IQR 0–3 days), 64 (7.7%) required orotracheal intubation, and 43 (5.2%) died.

Prevalence, intensity, and evolution of GI symptoms due to COVID-19

All patients presented in the emergency room due to fever and/or respiratory symptoms. Upon admission, 660 (73.3%) patients had at least one GI symptom, and 406 (49.0%) had two or more GI symptoms, when anorexia was considered a GI symptom. When excluding anorexia, 544 (65.6%) patients had at least one GI symptom and 299 (36.1%) presented two or more. All GI symptoms, except constipation, were more frequent at admission compared to baseline (before COVID-19) (Table 2). The most prevalent GI symptoms at admission were anorexia (n = 413; 49.8%), diarrhoea (n = 327; 39.4%), nausea/vomiting (n = 227; 27.4%), and abdominal pain (n = 172; 20.7%) (Table 2). Patients who reported diarrhoea had a median of 3 bowel movements/day (IQR 2–4), with a mean Bristol scale consistency of 6 (IQR 5–6). Patients with constipation had a median of 1 bowel movement/day (IQR 0–1), with a mean Bristol scale consistency of 2 (IQR 1–4). In most cases, the intensity of GI symptoms was mild or moderate (Table 2). In general, the prevalence and intensity of GI symptoms were maximal at admission and progressively decreased, returning to baseline pre-COVID-19 status between discharge and 15 days post-discharge (Fig. 1 and Table 2). GI symptoms at baseline did not significantly differ from those at discharge, between discharge and 15 days post-discharge, or at 15 days after discharge—with the exception that the frequency of diarrhoea was lower at 15 days after discharge compared to at baseline.

Development of GI complications due to COVID-19

GI complications were infrequent—except for acute liver injury or worsening of previous liver disease, which was present in 267 (32.1%) patients, 251 (94.0%) of whom already had it upon admission (supplementary content 2). Among the patients with liver damage, 238 (89.1%) presented mild hypertransaminasemia, 29 (10.9%) severe hypertransaminasemia, 246 (29.7%) elevated enzymes of cholestasis, 17 (6.4%) any increase of bilirubin level, and 2 (0.7%) an INR increase to >1.5 IU (not related to liver failure). Patients with liver injury exhibited the following median maximum values of liver laboratory parameters: aspartate-aminotransferase (AST) 63 (IQR 44–108) U/L, alanine-aminotransferase (ALT) 73 (IQR 50–135) U/L, gamma-glutamyl transpeptidase (GGT) 144 (IQR 102–267) U/L, alkaline phosphatase (AF) 146 (IQR 124–202) U/L, and bilirubin 1.6 (IQR 1.3–2.0) mg/dL. No patient developed acute liver failure. Supplementary content 2 summarizes other exceptional GI complications that occurred and their suspected causes.

Association between GI symptoms/complications and COVID-19 severity

Table 1 summarizes the baseline characteristics associated with severe COVID-19. Bivariate analysis revealed that severe COVID-19 was associated with dysphagia (OR 4.384; 95% CI 1.899–10.118; p < 0.001), odynophagia (OR 10.182; 95% CI 4.637–22.356; p < 0.001), and liver injury (OR 1.762; 95% CI 1.200–2.587; p = 0.004). In contrast, non-severe COVID-19 was associated with the presence of ≥2 gastrointestinal symptoms upon admission (OR 0.679; 95% CI 0.464–0.995; p = 0.046) and diarrhoea during hospitalization after adjustment for baseline diarrhoea (OR 0.531; 95% CI 0.328–0.860; p = 0.009) (Table 3).

Despite the associations revealed by bivariate analysis, multivariate analysis evaluating hospital outcomes showed that only odynophagia during hospitalization was an independent risk factor for ICU admission (aOR 7.038; 95% CI 1.900–26.068; p = 0.003) and mortality (aOR 9.942; 95% CI 1.523–64.875; p = 0.016) (Tables 4 and 5). GI symptoms and complications were not independently associated with hospital stay (p > 0.05) (Table 6).

A sub-analysis performed to evaluate possible confounding factors revealed that patients who presented with odynophagia and dysphagia during hospitalization (after adjustment for pre-COVID-19 symptoms) more frequently required orotracheal intubation during hospitalization: 8 (28.6%) patients with odynophagia versus 47 (6.0%) without odynophagia, and 8 (33.3%) patients with dysphagia versus 47 (6.0%) without dysphagia (p < 0.05). In contrast, odynophagia and dysphasia at admission did not predict poorer hospital outcomes (data not shown).

Discussion

To our knowledge, this is one of the first international prospective observational study designed specifically to evaluate the frequency of GI symptoms and complications in patients hospitalized due to COVID-19. We have particularly focused on assessing the presence of pre-COVID-19 GI symptoms, the patient-reported intensity of GI symptoms, and monitoring the evolution of these symptoms throughout the disease.

The most frequent COVID-19-related GI symptoms were anorexia, diarrhoea, nausea/vomiting, and abdominal pain,

Table 1 Basal characteristics and differences between severe and non-severe COVID-19, bivariate analysis.

Basal characteristics	Total $N = 829$	Severe COVID-19*, 129 (15.6)	Non-severe COVID-19, 689 (83.1)	Bivariate analysis			
				OR	95% CI		*p*
					Lowest	Highest	
Age, years	57 (44–70)	58 (48–71)	56 (43–69)	1.008	0.997	1.018	0.163
Gender, male	481 (58.0)	89 (69.0)	387 (56.3)	1.725	1.153	2.579	**0.007**
Active smoking	60 (7.2)	11 (8.5)	49 (7.1)	1.214	0.613	2.403	0.578
Active alcohol intake	122 (14.7)	17 (13.2)	105 (15.3)	0.841	0.485	1.459	0.538
BMI, kg/m²	28.2 (25.2–31.9)	29.1 (25.2–33.3)	28.2 (25.2–31.9)	1.027	0.996	1.059	0.130
Charlson Comorbidity Index	2 (0–4)	2 (1–4)	2 (0–3)	1.086	1.003	1.171	**0.030**
Comorbidities							
Arterial hypertension	325 (39.2)	56 (43.4)	263 (38.2)	1.243	0.849	1.818	0.263
Dyslipidaemia	185 (22.3)	24 (18.6)	156 (22.6)	0.781	0.484	1.260	0.310
Heart disease	90 (10.9)	11 (8.5)	59 (8.6)	0.995	0.508	1.951	0.989
Peripheral vascular disease	21 (2.5)	6 (4.7)	14 (2.0)	2.352	0.887	6.238	0.077
Cerebrovascular disease	28 (3.4)	6 (4.7)	19 (2.8)	1.720	0.673	4.394	0.263
Dementia	22 (2.7)	6 (4.7)	15 (2.2)	2.192	0.834	5.759	0.124
Chronic pulmonary disease	72 (8.7)	10 (7.8)	60 (8.7)	0.881	0.439	1.770	0.722
Thromboembolic disease	9 (1.1)	1 (0.8)	7 (1.0)	0.761	0.093	6.239	1.000
Connective tissue disease	11 (1.3)	2 (1.6)	9 (1.3)	1.190	0.254	5.572	0.688
Diabetes	187 (22.6)	42 (32.6)	141 (20.5)	1.876	1.242	2.833	**0.002**
Moderate–severe CRD, Cr >3 mg/dL	29 (3.5)	9 (7.0)	19 (2.8)	2.645	1.169	5.984	**0.016**
Any tumour without metastasis	34 (4.1)	5 (3.9)	29 (4.2)	0.918	0.348	2.417	0.862
Metastatic solid tumour	5 (0.6)	1 (0.8)	4 (0.6)	1.338	0.148	12.067	0.577
Leukaemia	7 (0.8)	2 (1.6)	5 (0.7)	2.154	0.413	11.226	0.305
Lymphoma	4 (0.5)	0 (0.0)	4 (0.6)	0.000	0.000	–	1.000
AIDS	4 (0.5)	0 (0.0)	3 (0.4)	0.000	0.000	–	1.000
Chronic treatments							
ARBs	160 (19.3)	26 (20.2)	130 (18.9)	1.085	0.678	1.738	0.733
ACE inhibitors	110 (13.3)	20 (15.5)	86 (12.5)	1.287	0.759	2.180	0.348
NSAIDs	45 (5.4)	3 (2.3)	41 (6.05)	0.376	0.115	1.234	0.133
Corticosteroids	29 (3.5)	2 (1.6)	26 (3.8)	0.402	0.094	1.713	0.292
Oral antidiabetics	149 (18.0)	29 (22.5)	118 (17.1)	1.403	0.887	2.219	0.146
Heparin	6 (0.7)	1 (0.8)	5 (0.7)	1.069	0.124	9.224	0.952
Insulin	61 (7.4)	17 (13.2)	43 (6.2)	2.280	1.256	4.140	**0.006**
Oral anticoagulants	47 (5.7)	11 (8.5)	32 (4.6)	1.914	0.939	3.903	0.070
Statins	165 (19.9)	20 (15.5)	139 (20.2)	0.726	0.435	1.211	0.219
Proton pump inhibitors	178 (21.5)	23 (17.8)	151 (21.9)	0.773	0.476	1.256	0.298
Previous GI disease							
Peptic ulcer	25 (3.0)	3 (2.3)	20 (2.9)	0.795	0.233	2.716	1.000
Gastroesophageal reflux	76 (9.2)	7 (5.4)	67 (9.7)	0.530	0.238	1.183	0.115
Eosinophilic esophagitis	1 (0.1)	0 (0.0)	1 (0.1)	0.000	0.000	–	1.000
Gastritis/duodenitis	15 (1.5)	0 (0.0)	14 (2.0)	0.000	0.000	–	0.143
Functional disorders	85 (10.3)	11 (8.5)	70 (10.2)	0.823	0.423	1.601	0.566
H. pylori-associated disease	34 (4.1)	1 (0.8)	31 (4.5)	0.166	0.022	1.226	0.078
Chronic liver disease**	47 (5.7)	6 (4.7)	40 (5.8)	0.791	0.328	1.907	0.835
Symptomatic cholelithiasis	36 (4.4)	3 (2.3)	32 (4.6)	0.489	0.147	1.621	0.342
Acute cholecystitis	16 (1.9)	1 (0.8)	15 (2.2)	0.351	0.046	2.681	0.490
Choledocholithiasis	2 (0.2)	0 (0.0)	2 (0.3)	0.000	0.000	–	1.000
Cholangitis	1 (0.1)	0 (0.0)	1 (0.1)	0.000	0.000	–	1.000
Acute pancreatitis	4 (0.5)	0 (0.0)	3 (0.4)	0.000	0.000	–	1.000
Chronic pancreatitis	1 (0.1)	0 (0.0)	1 (0.1)	0.000	0.000	–	1.000
Celiac disease	1 (0.1)	1 (0.8)	0 (0.0)	8.6×10^9	0.000	–	1.000

Table 1 (*Continued*)

Basal characteristics	Total *N* = 829	Severe COVID-19*, 129 (15.6)	Non-severe COVID-19, 689 (83.1)	Bivariate analysis			
				OR	95% CI		*p*
					Lowest	Highest	
Diverticulosis/diverticulitis	14 (1.7)	0 (0.0)	13 (1.9)	0.000	0.000	–	0.999
Inflammatory bowel disease	5 (0.6)	0 (0.0)	5 (0.7)	0.000	0.000	–	1.000
Cholangiocarcinoma	1 (0.1)	0 (0.0)	1 (0.1)	0.000	0.000	–	1.000
Hepatocellular carcinoma	1 (0.1)	1 (0.8)	0 (0.0)	8.6×10^9	0.000	–	1.000
Colorectal cancer	8 (1.0)	1 (0.8)	7 (1.0)	0.761	0.093	6.239	1.000

The values in bold are those results that have reached statistical significance (p < 0.05).
Data were missing or unavailable for 11 patients that could not be classified as having severe or non-severe COVID-19.
Qualitative variables expressed as absolute number (%). Quantitative variables expressed as mean and standard deviation (SD) or median and interquartile range (IQR). ACE inhibitors: angiotensin-converting enzyme inhibitors; AIDS: acquired immunodeficiency syndrome; ARBs: angiotensin II receptor blockers; BMI: body mass index; CI: confidence intervals; Cr: creatinine; CRD: chronic renal disease; *H. pylori*: *Helicobacter pylori*; IQR: interquartile range; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio.
* Severe COVID-19 was defined as the need for ICU admission, need for mechanical ventilation, and/or mortality during hospitalization.
** Types of chronic liver disease prior to COVID-19: non-alcoholic fatty liver disease 27 (42.6%); alcoholic liver disease 6 (12.8%), chronic VHB liver disease 8 (18.0%); chronic VHC liver disease 6 (12.8%); primary biliary cholangitis 1 (2.1%); idiopathic liver disease 2 (4.3%).

Table 2 Frequency and intensity of gastrointestinal symptoms.

Symptoms	Total *N* (%)	Mild *N* (%)	Moderate *N* (%)	Severe *N* (%)	*p* value[a]
Diarrhoea					
Before COVID-19	55 (6.6)	34 (4.1)	18 (2.2)	3 (0.4)	
At admission	327 (39.4)	169 (20.3)	128 (15.4)	30 (3.6)	**<0.001**
During hospitalization	263 (31.7)	174 (21.0)	82 (9.9)	7 (0.8)	**<0.001**
At discharge	74 (8.1)	67 (8.1)	7 (0.9)	0 (0.0)	1.0
From discharge to 15 days post-discharge	64 (7.7)	52 (6.3)	11 (1.3)	1 (0.1)	1.0
15 days post-discharge	33 (4.0)	29 (3.5)	3 (0.4)	1 (0.1)	**0.01**
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 21 (2.5%); at discharge: 23 (2.8%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Constipation					
Before COVID-19	71 (8.6)	42 (5.1)	22 (2.7)	7 (0.8)	
At admission	71 (8.6)	29 (3.5)	36 (4.3)	6 (0.7)	1.0
During hospitalization	117 (14.1)	53 (6.4)	48 (5.8)	16 (1.9)	**<0.001**
At discharge	87 (10.5)	56 (6.8)	22 (2.7)	9 (1.1)	1.0
From discharge to 15 days post-discharge	71 (8.6)	48 (5.8)	13 (1.6)	10 (1.2)	1.0
15 days post-discharge	47 (5.7)	29 (3.5)	15 (1.8)	3 (0.4)	1.0
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 22 (2.7%); at discharge: 23 (2.8%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Nausea & vomiting					
Before COVID	30 (3.6)	21 (2.5)	8 (1.0)	1 (0.1)	
At admission	227 (27.4)	134 (16.2)	75 (9.0)	18 (2.2)	**<0.001**
During hospitalization	140 (16.9)	104 (12.5)	32 (3.9)	4 (0.5)	**<0.001**
At discharge	32 (3.9)	28 (3.4)	4 (0.5)	0 (0.0)	1.0
From discharge to 15 days post-discharge	34 (4.1)	28 (3.4)	4 (0.5)	2 (0.2)	1.0
15 days post-discharge	20 (2.4)	18 (2.2)	1 (0.1)	1 (0.1)	0.3
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 22 (2.7%); at discharge: 23 (2.8%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Abdominal pain					
Before COVID	47 (5.7)	37 (4.5)	6 (0.7)	4 (0.5)	
At admission	172 (20.7)	92 (11.1)	63 (7.6)	17 (2.1)	**<0.001**
During hospitalization	141 (17.0)	96 (11.6)	41 (4.9)	4 (0.5)	**<0.001**

Table 2 (*Continued*)

Symptoms	Total *N* (%)	Mild *N* (%)	Moderate *N* (%)	Severe *N* (%)	*p* value[a]
At discharge	38 (4.6)	30 (3.6)	8 (1.0)	0 (0.0)	1.0
From discharge to 15 days post-discharge	55 (6.6)	44 (5.3)	7 (0.8)	4 (0.5)	1.0
15 days post-discharge	30 (3.6)	21 (2.5)	8 (1.0)	1 (0.1)	0.9
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 22 (2.7%); at discharge: 23 (2.8%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Anorexia					
Before COVID	73 (8.8)	50 (6.0)	15 (1.8)	8 (1.0)	
At admission	413 (49.8)	143 (17.2)	162 (19.5)	108 (13.0)	**<0.001**
During hospitalization	339 (40.9)	154 (18.6)	145 (17.5)	40 (4.8)	**<0.001**
At discharge	181 (21.8)	140 (16.9)	30 (3.6)	11 (1.3)	1.0
From discharge to 15 days post-discharge	113 (13.6)	85 (10.3)	23 (2.8)	5 (0.6)	1.0
15 days post-discharge	49 (5.9)	38 (4.6)	9 (1.1)	2 (0.2)	0.04
Missing data. Before COVID-19: 5 (0.6%); at admission: 4 (0.5%); during hospitalization: 22 (2.7%); at discharge: 23 (2.8%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Gas/bloating/flatulence					
Before COVID	63 (7.6)	51 (6.2)	12 (1.4)	0 (0.0)	
At admission	113 (13.6)	70 (8.4)	39 (4.7)	4 (0.5)	**<0.001**
During hospitalization	121 (14.6)	77 (9.3)	37 (4.5)	7 (0.8)	**<0.001**
At discharge	65 (7.8)	47 (5.7)	18 (2.2)	0 (0.0)	0.9
From discharge to 15 days post-discharge	85 (10.3)	76 (9.2)	9 (1.1)	0 (0.0)	0.2
15 days post-discharge	57 (6.9)	51 (6.2)	6 (0.7)	0 (0.0)	0.9
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 22 (2.7%); at discharge: 23 (2.8%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Odynophagia					
Before COVID	9 (1.0)	6 (0.7)	2 (0.2)	1 (0.1)	
At admission	49 (5.9)	28 (3.4)	17 (2.1)	4 (0.5)	**<0.001**
During hospitalization	29 (3.5)	20 (2.4)	7 (0.8)	2 (0.2)	**0.02**
At discharge	18 (2.2)	12 (1.4)	5 (0.6)	1 (0.1)	0.6
From discharge to 15 days post-discharge	6 (0.7)	3 (0.4)	2 (0.2)	1 (0.1)	1.0
15 days post-discharge	6 (0.7)	4 (0.5)	2 (0.2)	0 (0.0)	1.0
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 23 (2.8%); at discharge: 24 (2.9%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Heartburn/gastroesophageal reflux					
Before COVID	41 (4.9)	35 (4.2)	6 (0.7)	0 (0.0)	
At admission	61 (7.4)	38 (4.6)	19 (2.3)	4 (0.5)	**<0.001**
During hospitalization	51 (6.2)	38 (4.6)	11 (1.3)	2 (0.2)	0.5
At discharge	35 (4.2)	27 (3.3)	8 (1.0)	0 (0.0)	1.0
From discharge to 15 days post-discharge	43 (5.2)	32 (3.9)	8 (1.0)	3 (0.4)	1.0
15 days post-discharge	34 (4.1)	23 (2.8)	9 (1.1)	2 (0.2)	1.0
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 23 (2.8%); at discharge: 24 (2.9%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					
Dysphagia					
Before COVID	8 (1.0)	5 (0.6)	3 (0.4)	0 (0.0)	
At admission	22 (2.7)	11 (1.3)	9 (1.1)	2 (0.2)	**0.003**
During hospitalization	28 (3.5)	16 (1.9)	9 (1.1)	3 (0.4)	**0.003**
At discharge	21 (2.5)	16 (1.9)	4 (0.5)	1 (0.1)	0.08
From discharge to 15 days post-discharge	10 (1.2)	9 (1.1)	1 (0.1)	0 (0.0)	0.2
15 days post-discharge	7 (0.9)	6 (0.7)	1 (0.1)	0 (0.0)	0.6
Missing data. Before COVID-19: 4 (0.5%); at admission: 3 (0.4%); during hospitalization: 23 (2.8%); at discharge: 24 (2.9%); from discharge to 15 days post-discharge: 71 (8.6%); at 15 days post-discharge: 71 (8.6%).					

The values in bold are those results that have reached statistical significance ($p < 0.05$).

[a] Pairwise comparisons using Wilcoxon signed-rank test with continuity correction: each symptom during COVID-19 was compared to the pre-COVID-19 baseline presence of the symptom. Qualitative variables expressed as absolute number (%). Intensity during hospitalization and from discharge to 15 days post-discharge: higher intensity reported by the patient during those periods.

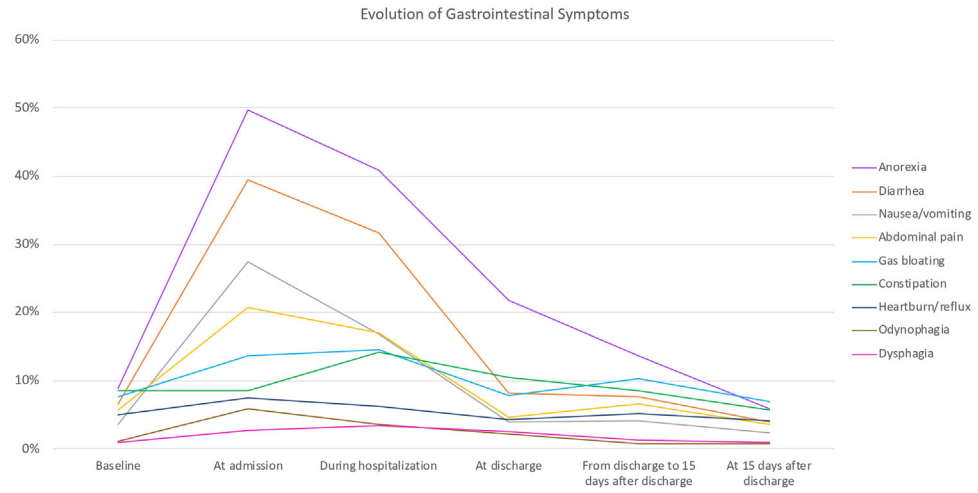

Figure 1 Frequency of gastrointestinal symptoms, from pre-COVID-19 baseline presence of the symptoms (baseline) to 15 days post-discharge.

as previously published.[2-5,20,21] However, our cohort presented a higher frequency of GI symptoms than has been earlier described in hospitalized patients. Among our patients, 74.3% presented at least one GI symptom, and 49.0% with two or more GI symptoms at the time of admission. In contrast, early retrospective published studies report prevalence rates of ∼10%,[2-4,21] and later publications report prevalence rates of up to 50%.[5,20] This disparity could be explained by previous studies' logical focus on respiratory symptoms, as well as their retrospective nature, with a bias towards more severe GI symptoms (as milder ones would not be included on clinical records), and the inherent design drawbacks of frequent data loss, low-quality assessments, and short follow-up.

Consistent with our results, among the few published prospective studies, the prevalence of GI symptoms were similar to ours. Thus, the prospective case–control studies by Marasco et al.,[22] including 871 patients (575 COVID+ and 296 COVID−), and Chen et al.,[23] including 340 patients (101 COVID+ and 239 COVID−), showed a significantly higher prevalence of GI symptoms ($p < 0.001$ both studies) in COVID-19 patients. This way, the prevalence of GI symptoms was 59.7% in the study by Marasco et al. vs 65.6% in our study (anorexia was not included as a symptom); and 74% in the study by Chen et al. vs 74.3% in ours (anorexia was included as a symptom). Although in this second study most of the patients were not hospitalized (different population), it is an obvious example of higher prevalence of GI symptoms reported in prospective studies focus specifically in them. By comparison, another Moroccan study involving 713 patients with COVID-19 described lower prevalences of GI symptoms (14.3%). In this case, the results are likely to be biased by the population included (64 children, 17 pregnant women, 30-years mean age of the cohort).[24]

Besides, in our study GI symptoms were mostly perceived as mild or moderate, as intuited by Elmunzer et al.,[5] tended to resolve early, similar to the study by Marasco et al.,[22] and were not associated with severe COVID-19 or worse hospital outcomes (understood as need for ICU admission, longer hospital stay or death). Thus, contrary to speculations of the earliest studies,[4] our present findings suggest that GI symptoms are mild manifestations of COVID-19 that do not predict a more aggressive course,[5,25] and point that persistent GI symptoms due to COVID-19 are very rare.

Only odynophagia and dysphagia during hospitalization were associated with poorer outcomes. However, a subanalysis revealed that patients reporting these symptoms more frequently required orotracheal intubation during admission, such that they may be a consequence of this invasive treatment.

Future studies should be directed to elucidate whether these symptoms are due to the direct effect of the virus, secondary aspects of the disease (e.g., odynophagia due to incubation, constipation due to immobility) or adverse effects of the medication.

Regarding GI complications, our study population showed no cases of cholecystitis, pancreatitis, enteritis, duodenitis, cholangitis, debut of inflammatory bowel disease, or GI vascular complications—contrary to the findings of some retrospective studies.[12,13,16,17,26–29] Special attention should be paid to acute or worsening liver injury, which affected up to 1/3 of the included patients and mainly presented as mild hypertransaminasemia,[3–5] consistent with the suggestions of retrospective studies.[10,29,30] Furthermore, bivariate analysis showed that liver injury was more prevalent in patient with severe COVID-19, need for ICU admission, large hospital stay, and mortality. However, when adjusting this condition for other potential confounders, liver injury was not an independent predictor of worse hospital outcomes, in contrast to the suggestions of previous studies.[5,10,31,32] It is worth mentioning, Weber et al. found that increased risk of ICU admission was associated with any abnormal liver parameter, after adjusting for age, gender, and relevant comorbidities.[32] This difference could be explained by the variables considered in the logistic regression. In our study, these variables also included respiratory symptoms, organ failure, and inflammation, which seem to be the main determinants of disease severity in our cohort. Despite these results, more studies focused on liver damage should be performed to clarify this possible association and the etiopathogenesis of liver injury.

Table 3 Associations of symptoms and complications and other outcome variables with COVID-19 severity; bivariate analysis.

Variables	Total *N* = 829 (%)	Severe COVID-19*, 129 (15.6%)	Non severe COVID-19, 689 (83.1%)	Bivariate analysis			
				OR	95% CI		*p*
					Lowest	Highest	
Treatments							
Hydroxychloroquine	42 (5.1)	3 (2.3)	39 (5.7)	0.396	0.121	1.302	0.131
Azithromycin	331 (39.9)	65 (50.4)	265 (38.5)	**1.621**	1.111	2.365	**0.012**
Lopinavir/ritonavir	82 (9.9)	7 (5.4)	75 (10.9)	0.469	0.211	1.042	0.058
Tocilizumab	81 (9.8)	16 (12.4)	65 (9.4)	1.357	0.758	2.430	0.303
Anakinra	3 (0.4)	2 (1.6)	1 (0.1)	10.819	0.974	120.206	0.067
Steroids	549 (66.2)	115 (89.1)	429 (62.3)	**4.959**	2.788	8.820	**<0.001**
GI symptoms at admission							
1 GI symptom	616 (74.3)	98 (76.0)	510 (74.0)	1.097	0.708	1.701	0.679
≥2 GI symptoms	406 (49.0)	53 (41.1)	348 (50.5)	**0.679**	0.464	0.995	**0.046**
Type of GI symptom							
Abdominal pain	123 (14.8)	17 (13.2)	105 (15.2)	0.919	0.528	1.599	0.765
Nausea/vomiting	128 (15.5)	13 (10.1)	112 (16.3)	0.626	0.340	1.153	0.130
Anorexia	298 (35.9)	48 (37.2)	248 (36.0)	1.186	0.796	1.766	0.401
Diarrhoea	237 (28.6)	23 (17.8)	213 (30.9)	**0.531**	0.328	0.860	**0.009**
Constipation	90 (10.9)	11 (8.5)	79 (11.5)	0.780	0.402	1.514	0.462
Gas/bloating/flatulence	92 (11.1)	9 (7.0)	81 (11.8)	0.609	0.297	1.249	0.172
Dysphagia	24 (2.9)	10 (7.8)	14 (2.0)	**4.384**	1.899	10.118	**<0.001**
Odynophagia	28 (3.4)	17 (13.2)	11 (1.6)	**10.182**	4.637	22.356	**<0.001**
Heartburn/GE reflux	34 (4.1)	6 (4.7)	28 (4.1)	1.242	0.503	3.067	0.638
Respiratory symptoms							
Dyspnoea	430 (51.9)	101 (78.3)	329 (47.8)	**5.736**	3.436	9.576	**<0.001**
Cough	480 (57.9)	89 (69.0)	390 (56.6)	**2.172**	1.404	3.358	**<0.001**
Expectoration	147 (17.7)	33 (25.6)	114 (16.5)	**1.900**	1.213	2.95	**0.005**
Other non-GI symptoms							
Ageusia	195 (23.5)	26 (21.7)	167 (24.4)	0.856	0.536	1.367	0.516
Anosmia	177 (21.4)	22 (18.3)	154 (22.5)	0.773	0.470	1.269	0.307
Disorientation	75 (9.0)	35 (29.2)	40 (5.8)	**6.640**	4.000	11.023	**<0.001**
Decreased level of consciousness	71 (8.6)	37 (30.8)	34 (5.0)	**8.535**	5.081	14.337	**<0.001**
Headache	228 (27.5)	37 (30.8)	190 (27.7)	1.161	0.762	1.771	0.487
Myalgia	254 (30.6)	32 (26.7)	221 (32.3)	0.763	0.494	1.180	0.223
Skin lesions	25 (3.0)	2 (1.7)	23 (3.4)	0.488	0.114	2.097	0.565
Fever	259 (31.2)	59 (49.2)	200 (29.2)	**2.345**	1.582	3.478	**<0.001**
Liver damage, SOFA score, and CRP							
Liver damage	267 (32.2)	56 (43.4)	209 (30.3)	**1.762**	1.200	2.587	**0.004**
Deep vein thrombosis	7 (0.8)	3 (2.3)	4 (0.6)	4.077	0.902	18.438	0.083
Pulmonary thromboembolism	26 (3.1)	4 (3.1)	22 (3.2)	0.970	0.329	2.864	1.000
New onset arrhythmia	15 (1.8)	8 (6.2)	7 (1.0)	**6.442**	2.294	18.091	**0.001**
SOFA score (points)	1 (0–2)	4 (2–6)	1 (0–2)	**6.852**	5.025	9.344	**<0.001**
CRP mg/dL	6.3 (2.0–14.0)	12.7 (5.3–24.5)	5.6 (1.7–12.4)	**1.010**	1.003	1.017	**<0.001**
Hospital stay length							
Hospital stay length	8 (5–12)	13 (9–20)	7 (5–10)	**1.112**	1.083	1.143	**<0.001**

The values in bold are those results that have reached statistical significance ($p < 0.05$).
Data were missing or unavailable data for 11 patients who could not be classified as having severe or non-severe COVID-19.
GI symptoms were adjusted by the baseline pre-COVID-19 presence of the symptoms, eliminating those cases in which the symptom presented before COVID-19. Qualitative variables expressed as absolute number (%). Quantitative variables expressed as mean and standard deviation (SD) or median and interquartile range (IQR). CI: confidence interval; CRP: C-reactive protein; GE reflux: gastroesophageal reflux; GI: gastrointestinal; OR: odds ratio; SOFA score: sepsis-related organ failure assessment score.
* Severe COVID-19 was defined as a need for ICU admission, need for mechanical ventilation, and/or mortality during hospitalization.

Table 4 Multivariate analysis assessing the association between intensive care unit admission and possible determinants.

Need for ICU admission, *N* = 113 (13.7%)							
	ICU	Not ICU	Bivariate	Multivariate			
			p	aOR	95% CI		*p*
					Lowest	Highest	
Age, years	55 (47–66)	57 (43–70)	0.510	0.982	0.954	1.010	0.209
Sex, male	79 (70.5)	399 (56.3)	**0.004**	0.895	0.471	1.701	0.735
Charlson Index, points	2 (1–4)	2 (0–4)	0.673	0.846	0.666	1.073	0.167
BMI, kg/m^2	29.3 (25.5–33.6)	28.1 (25.2–31.8)	**0.035**	1.031	0.983	1.080	0.207
Alcohol intake	15 (13.3)	107 (15.1)	0.614	0.944	0.405	2.198	0.893
Smoking	10 (8.8)	50 (7.1)	0.495	0.932	0.292	2.972	0.905
Abdominal pain	12 (11.5)	111 (15.8)	0.258	0.604	0.225	1.624	0.318
Nausea/vomiting	11 (10.6)	117 (16.7)	0.113	0.515	0.202	1.311	0.164
Anorexia	40 (38.5)	258 (36.8)	0.744	0.859	0.457	1.613	0.636
Diarrhoea	21 (20.2)	216 (30.7)	**0.028**	0.938	0.447	1.969	0.866
Constipation	8 (7.7)	82 (11.7)	0.228	0.784	0.296	2.076	0.624
Abdominal bloating	7 (6.7)	85 (12.1)	0.108	0.386	0.111	1.342	0.134
Dysphagia	9 (8.7)	15 (2.1)	**0.002**	2.835	0.818	9.831	0.100
Odynophagia	15 (14.4)	13 (1.9)	**<0.001**	7.038	1.900	26.068	**0.003**
Heartburn/reflux	5 (4.8)	29 (4.1)	0.792	0.565	0.137	2.325	0.429
Dyspnoea	87 (82.9)	343 (48.9)	**<0.001**	2.878	1.342	6.172	**0.007**
Cough	76 (72.4)	404 (57.5)	**0.004**	0.943	0.469	1.896	0.869
Expectoration	26 (24.8)	121 (17.2)	0.061	0.789	0.353	1.764	0.564
Liver damage	51 (46.4)	214 (30.2)	**0.001**	1.013	0.540	1.899	0.968
SOFA score, points	4 (2–6)	1 (0–2)	**<0.001**	5.115	3.494	7.486	**0.000**
CRP, mg/dL	14.2 (7.8–25.1)	5.5 (1.7–12.4)	**<0.001**	1.010	1.002	1.018	**0.014**

The values in bold are those results that have reached statistical significance ($p < 0.05$).
Analysis included 751 patients with no missing data for any of the variables. R^2 Nagelkerke: 50.1%.
GI symptoms were adjusted by the baseline pre-COVID-19 presence of the symptoms, eliminating cases in which the symptom presented before COVID-19. Qualitative variables expressed as absolute number (%). Quantitative variables expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Sex representing the biological sex. BMI: body mass index; CI: confidence intervals; CRP: C-reactive protein; OR: odds ratio; SOFA score: sepsis-related organ failure assessment score.

Table 5 Multivariate analysis assessing the association between mortality and possible determinants.

Mortality during hospitalization, *N* = 43 (5.2%)							
	Death	Not death	Bivariate	Multivariate			
			p	aOR	95% CI		*p*
					Lowest	Highest	
Age, years	72 (58–85)	56 (43–68)	**<0.001**	1.098	1.041	1.159	**0.001**
Sex, male	32 (74.4)	446 (57.5)	**0.028**	4.343	1.072	17.600	**0.040**
Charlson Index, points	4 (2–6)	2 (0–3)	**<0.001**	1.030	0.954	1.112	0.445
BMI, kg/m^2	27.2 (24.8–30.2)	28.4 (25.3–32.0)	0.162	1.002	0.883	1.138	0.976
Alcohol intake	2 (4.7)	120 (15.5)	**0.049**	0.496	0.070	3.487	0.481
Smoking	5 (11.6)	55 (7.1)	0.235	8.901	0.817	96.925	0.073
Abdominal pain	7 (19.4)	115 (15.0)	0.467	0.517	0.066	4.053	0.530
Nausea/vomiting	4 (11.1)	121 (15.8)	0.638	1.102	0.175	6.957	0.918
Anorexia	11 (30.6)	285 (37.2)	0.419	0.278	0.068	1.134	0.074
Diarrhoea	8 (22.2)	228 (29.7)	0.336	4.221	0.960	18.563	0.057
Constipation	2 (5.6)	88 (11.5)	0.416	0.799	0.100	6.374	0.832
Abdominal bloating	0 (0.0)	90 (11.7)	**0.026**	0.000	0.000	–	0.996
Dysphagia	0 (0.0)	24 (3.1)	0.620	0.000	0.000	–	0.997
Odynophagia	5 (13.9)	23 (3.0)	**0.006**	9.942	1.523	64.875	**0.016**
Heartburn/reflux	0 (0.0)	34 (4.4)	0.395	0.000	0.000	–	0.997

Table 5 (*Continued*)

Mortality during hospitalization, *N* = 43 (5.2%)							
	Death	Not death	Bivariate	Multivariate			
			p	aOR	95% CI		*p*
					Lowest	Highest	
Dyspnoea	33 (91.7)	397 (51.7)	**<0.001**	9.339	1.278	68.235	**0.028**
Cough	28 (77.8)	451 (58.6)	**0.022**	2.520	0.531	11.951	0.245
Expectoration	9 (25.0)	138 (17.9)	0.284	0.919	0.221	3.821	0.907
Liver damage	20 (46.5)	247 (31.7)	**0.044**	0.705	0.195	2.555	0.595
SOFA score, points	6 (4–6)	1 (0–2)	**<0.001**	6.448	3.479	11.951	**<0.001**
CRP, mg/dL	9.8 (3.1–18.1)	6.2 (2.0–13.6)	0.057	0.937	0.878	1.000	**0.050**

The values in bold are those results that have reached statistical significance (p < 0.05).
Analysis included 751 patients with no missing data for any of the variables. R^2 Nagelkerke: 65.8%.
GI symptoms were adjusted by the baseline pre-COVID-19 presence of the symptoms, eliminating cases that presented the symptom before COVID-19. Qualitative variables expressed as absolute number (%). Quantitative variables expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Sex representing the biological sex. BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; OR: odds ratio; SOFA score: sepsis-related organ failure assessment score.

Table 6 Bivariate and multivariate analyses assessing the association between length of hospital stay and possible determinants.

Length of hospitalization >8 days, *N* = 347 (41.9%)							
	>8 days	<8 days	Bivariate	Multivariate			
			p	aOR	95% CI		*p*
					Lowest	Highest	
Age, years	61 (49–73)	54 (41–66)	**<0.001**	1.011	1.000	1.022	**0.042**
Sex, male	207 (60.0	269 (56.9)	0.370	0.908	0.647	1.273	0.574
Charlson Index, points	2 (1–4)	1 (0–3)	**<0.001**	1.019	0.973	1.067	0.429
BMI, kg/m^2	28.2 (25.2–31.9)	28.3 (25.3–32.0)	0.916	1.013	0.986	1.042	0.344
Alcohol intake	40 (11.6)	82 (17.3)	**0.022**	0.662	0.410	1.067	0.090
Smoking	20 (5.8)	40 (8.5)	0.147	0.698	0.356	1.372	0.297
Abdominal pain	47 (14.1)	76 (16.1)	0.430	0.860	0.525	1.408	0.549
Nausea/vomiting	49 (14.7)	79 (16.7)	0.429	0.790	0.489	1.275	0.334
Anorexia	123 (36.9)	175 (37.1)	0.968	0.995	0.700	1.414	0.976
Diarrhoea	90 (26.9)	147 (31.1)	0.204	1.086	0.747	1.579	0.664
Constipation	35 (10.5)	55 (11.7)	0.602	0.714	0.421	1.209	0.210
Abdominal bloating	35 (10.5)	57 (12.1)	0.482	0.786	0.453	1.363	0.392
Dysphagia	16 (4.8)	8 (1.7)	**0.011**	2.020	0.753	5.416	0.163
Odynophagia	18 (5.4)	10 (2.1)	**0.012**	2.152	0.817	5.670	0.121
Heartburn/reflux	17 (5.1)	17 (3.6)	0.296	1.543	0.713	3.336	0.271
Dyspnoea	203 (60.6)	227 (48.1)	**<0.001**	1.360	0.957	1.934	0.086
Cough	186 (55.5)	294 (62.2)	0.059	0.573	0.400	0.821	**0.002**
Expectoration	65 (19.4)	82 (17.3)	0.453	1.119	0.712	1.760	0.626
Liver damage	127 (37.0)	137 (29.0)	**0.015**	1.202	0.844	1.711	0.308
SOFA score, points	2 (0–2)	1 (0–1)	**<0.001**	1.953	1.551	2.460	**<0.001**
CRP, mg/dL	7.3 (2.4–16.2)	5.7 (1.7–12.4)	**0.002**	1.004	0.997	1.010	0.255

The values in bold are those results that have reached statistical significance (p < 0.05).
Analysis included 751 patients with no missing data for any of the variables. R^2 Nagelkerke:17.8%.
GI symptoms were adjusted by the baseline pre-COVID-19 presence of the symptoms, eliminating cases in which the symptom presented before COVID-19. Qualitative variables expressed as absolute number (%). Quantitative variables expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Sex representing the biological sex. BMI: body mass index; CI: confidence intervals; CRP: C-reactive protein; OR: odds ratio; SOFA score: sepsis-related organ failure assessment score.

The strengths of this study include its international multicentre nature and its prospective design with a large sample size (higher number of COVID-19 patients included than other prospective studies). Additionally, it was specifically designed to study GI symptoms, assessed using comprehensive questionnaires that enabled proper evaluation of their frequency and intensity as perceived by patients. Finally, the prevalence of GI symptoms at each time point evaluated was compared with the baseline situation of patients, before COVID-19 (not with a control group without COVID, but with other pathologies requiring admission or follow-up in a health centre), allowing us to better discern the magnitude of symptoms caused by COVID-19. A weakness of this study is that the patient sample may be underpowered to detect rare COVID-19 gastrointestinal complications.

In conclusion, GI symptoms were more common than previously documented in hospitalized COVID-19 patients. They mostly presented as mild to moderate and tended to rapidly resolve. Our findings suggest that GI symptoms are a mild manifestation of COVID-19 that do not predict severity. Their isolated presentation as a cause of admission is exceptional, and its persistence outside the acute episode is very rare. Our results also sustain that liver injury is a prevalent complication among hospitalized patients while the rest of digestive complications previously described in the context of COVID-19 seem to be infrequent.

Authors' contributions

All authors were involved in data acquisition and critical revision of the manuscript. E. de-Madaria and K. Cárdenas-Jaén conceptualized and designed the study. A. Vaillo monitored the study. K. Cárdenas-Jaén, J.J. Mira, A. Mula, I. Carrillo, and E. de-Madaria performed the primary analysis and interpretation of the data. K. Cárdenas-Jaén, S.A. Sánchez-Luna, J.J. Mira, A. Mula, I. Carrillo, and E. de-Madaria prepared the initial draft of the manuscript. All authors have approved the final version of the manuscript.

Funding

This project received financial support from the Alicante Institute for Health and Biomedical Research (ISABIAL) (reference 2020-0355). Karina Cárdenas-Jaén was supported by a Río Hortega research contract from the Instituto de Salud Carlos III, Madrid, Spain, (reference CM19/00157).

Competing interests

The authors declare no conflict of interests for this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gastrohep.2022.10.007.

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